As can be seen, Blumbergs' statement that "a final recrystallization was necessary" comes in the context of the nature of an intermediate part which was produced in a step which involved extensive handling. Because of such handling, the product contained the mentioned impurities which, thus, had to be removed. The common impurity removal technique of recrystallization was thus applied. Clearly, Blumbergs is specifically stating that in his particular process at the mentioned stage of preparation, conventional recrystallization was necessary in an effort to remove impurities.

However, the passage goes on to state that the recrystallization resulted in "no real improvement in purity." This alone makes it impossible that Blumbergs can be teaching a skilled worker that recrystallizations are necessary in any situation. In fact, Blumberg goes on in the very next sentence to say that, instead of recrystallization, careful handling in the step at issue could be used whereby "recrystallization can be avoided."

Clearly, Blumbergs is not teaching the necessity of recrystallization when preparing fludarabine phosphate. Rather, it states that recrystallization was employed in the particular process involved and it failed, whereupon the reference suggests avoiding recrystallization.

Consequently, in no way can Blumbergs be combined with anything, including the Butler reference, to motivate a skilled worker to recrystallize fludarabine phosphate in an effort to improve its purity. The only rational conclusion from Blumbergs is that recrystallization is to be avoided, as explicitly stated in the passage at issue. On the basis alone, the rejection, it is respectfully submitted, can be seen to be unsound.

In the previous office action of February 7, 2007, the examiner relied on the processing disclosed by Butler from "column 5, lines 44-67 and column 6, lines 1-18." See page 4, second full paragraph of the office action. Applicants pointed out that this processing is a recrystallization and, thus, in combination with Blumbergs would never be utilized by a skilled worker. Applicants further pointed out that, despite this, even if a skilled worker did utilize the relied on processing to attempt to purify fludarabine phosphate, this would not work. The latter fact was proven by reference to the Wessa and Rabe declaration of record showing what happens at various pH conditions.

The examiner now states that a skilled worker would somehow be motivated to avoid the acidic conditions utilized in the previously relied-on passage and instead would look elsewhere in Butler for some other kind of recrystallization technique which did not apparently utilize acidic conditions. Thus, the examiner now newly relies on processing conditions disclosed in Butler at column 5, lines 36-46.

However, the examiner does not explain why a skilled worker would be motivated to apply such processing conditions in an effort to purify fludarabine phosphate. In fact, all facts of record indicate that a skilled worker would never be motivated to apply such processing.

Firstly, the relied-on passage also involves a recrystallization as the examiner acknowledges. As explained above, the relied on Blumbergs reference expressly teaches away from utilizing recrystallization techniques. Moreover, the processing now relied on is merely a particular step in the midst of a process of preparing a final product. The reference in no way indicates that this particular step leads to any purification of any significance. In fact, the immediately subsequent processing is the very disclosure relied on in the last office action by the examiner. That is, the newly relied on step from Butler is immediately followed in Butler by subsequent recrystallization expressly stated to be applied for purposes of achieving greater purity. See, e.g., column 5, lines 55-57. Note that the purity achieved before this additional recrystallization processing is utilized (previously relied on by the examiner) is only 85.24% wt/wt, far below that recited in the claims of this application. Clearly, when seeking to arrive at a purity of at least 99.5%, a skilled worker would be expressly taught by Butler to apply the previously relied-on processing which the examiner now agrees would be avoided by a skilled worker. See the end of the first full paragraph on page 5 of the last office action.

It is believed clear from the foregoing that the rejection must be withdrawn.

Finally, in the paragraph bridging pages 4 and 5 of the office action, the examiner refers to certain aspects of the Wessa and Rabe declaration. In this regard, it must be remembered that the experiments of this declaration, in part, were designed to rebut other experiments performed by opposers in the oppositions to the corresponding European patent. Thus, the attempt to prepare crystals reported in the declaration and mentioned by the examiner reflects an attempt to reproduce allegations of an opposer regarding its own ability to prepare crystals of certain purity. It is not relevant here at all as to whether such crystals could or could not be prepared. If they could not be prepared, this would in actuality reinforce the nonobviousness of the invention as it would reinforce the already established high level of difficulty (in essence, impossibility) of preparing fludarabine phosphate of the recited purity using conventional methods.

Recent Federal Circuit Decision

In *Aventis Pharma Deutschland GmbH v. Lupin*, __*F.3d*__ *(Fed.Cir. 2007)*, the Federal Circuit stated:

> The analysis is similar where, as here, a claimed composition is a purified form of a mixture that existed in the prior art. Such a purified compound is not always prima facie obvious over the mixture; for example, it may not be known that the purified compound is present in or an active ingredient of the mixture, or the state of the art may be such that discovering how to perform the purification is an invention of patentable weight in itself.

In this case, USP 6,046,322 which issued from the parent application, is drawn to such "an invention of patentable weight in itself." Moreover, the record is replete with proof of the high difficulty (actually, impossibility) of achieving fludarabine phosphate of the recited purity in crystalline form. Consequently, all claims should be allowed.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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